CLINICAL EVIDENCE

Infectious diseases: meningococcal disease

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QUESTIONS: What are the effects of prophylactic antibiotics on risk of disease in people exposed to someone with meningococcal disease? What are the effects of antibiotics in people with throat carriage of meningococcal disease?

Summary points

- We found no randomized evidence about the effects of antibiotics on the incidence of meningococcal disease among contacts. Observational data suggest that antibiotics reduce the risk of disease. We found no good evidence to address the question of which contacts should be treated.
- Randomized controlled trials have found that antibiotics reduce throat carriage of the meningococcus. We found no evidence that eradicating throat carriage reduces the risk of meningococcal disease.

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INTERVENTIONS

In descending order of effectiveness

Prophylactic antibiotics in contacts

Antibiotics for throat carriage (reduce carriage, but unknown effect on risk of disease)

Vaccines (monovalent/multivalent; polysaccharide alone, or conjugate)

Empiric treatment of suspected meningococcal disease

Treatment of meningococcal disease

DEFINITION

Meningococcal disease is any clinical condition caused by *Neisseria meningitidis* (the meningococcus) groups A, B, C, or other serogroups. These conditions include purulent conjunctivitis, septic arthritis, meningitis, and septicemia with or without meningitis.

INCIDENCE/PREVALENCE

Meningococcal disease is sporadic in temperate countries and is most commonly caused by group B or C meningococci. The incidence in the United Kingdom varies from 2 to 8 cases per 100,000 people per year[1] and in the United States from 0.6 to 1.5 per 100,000 population.[2] Occasional outbreaks occur among close family contacts, secondary school pupils, and students living in student housing. Sub-Saharan Africa has regular epidemics caused by serogroup A, particularly in countries lying between Gambia in the west and Ethiopia in the east (the "meningitis belt"), where the incidence during epidemics reaches 500 per 100,000.[3]

ETIOLOGY/RISK FACTORS

Meningococcus infects healthy people and is transmitted by close contact, probably by exchange of upper respiratory tract secretions (table 1).[4-12] Risk of transmission is greatest in the first week of contact.[7] Risk factors include crowding and exposure to cigarette smoke.[13] Children younger than 2 years have the highest incidence, with a second peak between ages 15 and 24 years. Currently an increased incidence of meningococcal disease is being seen among university students, especially among those in their first term and living in catered accommodations,[14] although we found no accurate numeric estimate of risk from close contact in, for example, halls of residence. Close contacts of an index case have a much higher risk of infection than people in the general population.[7,10,11] The risk of epidemic spread is higher with group A and C meningococci than with group B meningococci.[4,6,8] What makes a meningococcus virulent is not known, but certain clones tend to predominate at different times and in different groups. Carriage of meningococcus in the throat has been reported in 10% to 15% of people; recent acquisition of a virulent meningococcus is more likely to be associated with invasive disease.

PROGNOSIS

Mortality is highest in infants and adolescents and relates to disease presentation,[15-17] Case-fatality rates in septicemia range from 19% to 25%; in meningitis plus septicemia, from 10% to 12%; and in meningitis alone, less than 1%.[15-17]

AIMS

To prevent disease in contacts.

Table 1 *Risk of infection among contacts*

Group of meningococcus	Setting	Relative risk (RR)
A	Household contacts in Milwaukee, WI[4]	AR 1,100/100,000; RR not possible to estimate
	General population in Santiago province, Chile, household contacts[5]	Attack rate in general population 23-261.6/100,000 (1941 and 1942) Attack rate in household contacts 250/100,000 (2.5%) over both years
	General population in Indianapolis, IN[6]	AR 4,500/100,000; RR not possible to estimate
B	Household contacts in Belgium[7]	RR 1245*
	Nursery schools[7]	RR 23*
	Day care centers[7]	RR 76*
C	Household contacts from 2 lower socioeconomic groups, Dade County, FL[8]	Attack rate in 2 communities, 13/100,000 population; attack rate in household contacts, 5/85 (582/100,000)
Unspecified	School-based clusters in US; predominant meningococcal types: 13 clusters of GpC, 7 of GpB, 1 of GpY, 1 of CpC/W135 (impossible to distinguish)[9]	RR 2.3*
	Household contacts from several states in US, meningococcus types B and C predominantly[10]	RR 500-800*
	Household contacts in Norway; meningococcus types A, B, and C predominantly[11]	RR up to 4,000*
	Schools; predominant meningococcus type C[12]	OR 14.1 (95% CI, 1.6-127)

AR = absolute risk; OR = odds ratio; CI = confidence interval.
*Compared with the risk in the general population.

OUTCOMES

Rates of infection, rates of eradication of throat carriage, and adverse effects of treatment.

METHODS

The author searched by MEDLINE and BIDS in December 1998 and drew from a collection of references from the pre-electronic data era. All studies were considered for inclusion. *Clinical Evidence* search and appraisal November 1999.

QUESTION: What are the effects of prophylactic antibiotics on the risk of disease in people exposed to someone with meningococcal disease?

We found no randomized evidence of the effects of antibiotics on the incidence of meningococcal disease among contacts. Observational data suggest that taking antibiotics reduces the risk of disease. We found no good evidence to address the question of which contacts should be treated.

Benefits

We found no systematic review and of randomized controlled trials (RCTs) examining the effect of prophylactic antibiotic use in people who have been in contact with someone with meningococcal disease. **Rifampin [Rifampicin]:** We found only anecdotal data. **Penicillin:** We found 1 retrospective study whose results cannot be generalized beyond the sample tested.[18] **Sulfadiazine:** One observational cohort study of soldiers in temporary troop camps in the 1940s compared the incidence of meningococcal disease in camps where sulfadiazine was given to everyone after a meningoccocal outbreak versus the incidence in camps where no prophylaxis was given. The study reported a higher incidence of meningococcal disease in the comparison camps (approximate figures, 2/7,000 vs 17/9,500 over 8 weeks).[19]

Harms

Rifampin: No excess adverse effects compared with placebo were found in RCTs on throat carriage of meningococcal disease.[20,21] However, rifampin is known to turn urine and contact lenses orange and to induce hepatic microsomal enzymes, potentially rendering oral contraception ineffective. Rifampin prophylaxis may be associated with the emergence of resistant strains.[22] **Sulfadiazine:** One of 10 study participants experienced minor adverse events, including headache, dizziness, tinnitus, and nausea.[19]

Comment

RCTs addressing this question are unlikely to be performed because the intervention has few associated risks,

Table 2 *Effect of antibiotics on throat carriage: results of placebo-controlled randomized controlled trials*

Antibiotic	Group of meningococcus	Participants	Eradication		RR (95% CI)
			Treatment, No. (%)	Placebo, No. (%)	
Rifampin (oral)[20]	B, X, Z	30 students with heavy growth on culture	11/15 (73)	2/15 (13)	5.5 (1.46-20.7)
Rifampin (oral)[21]	B, C, Y, Z29 E, W135, NT	76 airforce recruits	36/38 (95)*	3/22 (14)†	6.95 (5.77-8.12)
Minocycline (oral)[23]	Predominantly Y (63%)	149 naval recruits	37/31 (90)‡	14/48 (29)§	3.09 (2.55-3.63)
Ciprofloxacin (oral)[24]	Nongroupable (61%), B (17.5%)	120 army recruits in Finland	54/56 (97), 5 second specimens missing	7/53 (13), 6 second specimens missing or not a carrier	7.3 (6.52-8.08)
Ciprofloxacin (oral)[25]	B (41%), Z (33%)	46 health volunteers	22/23 (96)‖	2/22 (9)	10.52 (8.91-12.1)

RR = relative risk; CI = confidence interval.
*Nine lost to follow-up.
†Twenty-three either did not have meningococci before therapy or did not provide a full set of cultures.
‡Thirty-seven either did not have meningococci before therapy or did not provide a full set of cultures.
§Seven were unavailable for follow-up.
‖One did not adhere to treatment.

and meningitis has high associated risks. RCTs would also need to be large to find a difference in the incidence of meningococcal disease. In the sulfadiazine cohort study, the 2 infected people in the treatment group became infected only after leaving the camp.[19]

QUESTION: What are the effects of antibiotics in people with throat carriage of meningococcal disease?

RCTs have found that antibiotic therapy reduces throat carriage of meningococcus. We found no evidence that eradicating throat carriage reduces the risk of meningococcal disease.

Benefits

We found no systematic review. **Incidence of disease:** We found no RCTs or observational studies examining whether eradicating throat carriage of meningococcus reduces the risk of meningococcal disease. **Throat carriage:** We found 5 placebo-controlled RCTs examining the effect of antibiotics on the carriage of meningococcus in the throat (table 2).[20,21,23-25] All studies reported that antibiotics—rifampin, minocycline hydrochloride, or ciprofloxacin hydrochloride—achieved high rates of eradication (ranging from 90%-97%), except 1 trial of rifampin in students with heavy growth on culture, where the rate of eradication was 73%. Eradication rates with placebo ranged from 9% to 29%. We found 6 RCTs comparing different antibiotic regimens (table 3).[26-31] Two RCTs found no significant difference between rifampin and either minocycline, ciprofloxacin, or intramuscular ceftriax-

Table 3 *Effect of antibiotics on throat carriage: results of comparative randomized controlled trials*

Antibiotic and route	Group of meningococcus	Participants	Rate of eradication, No. (%)	RR (95% CI)*
Penicillin, IM[26]	C (49%), B (33%), NG (17%)	Adults	41/118 (35)	
Erythromycin, oral[26]	C	Adults	0/7 (0)	
Rifampin, oral[27]	B plus C (31%), NG (69%)	Adults	43/51 (84)	0.89 (0.76-1.02)
Minocycline, oral[27]	B plus C (31%), NG (69%)	Adults	36/38 (95)	
Rifampin, oral[27]	A	Children	37/48 (77)	
Sulfadimidine, oral†[28]	A	Children	0/34 (0)	
Ceftriaxone, IM[29]	A	Adults and children	66/68 (97)	1.29 (1.10-1.49)
Rifampin, oral[29]	A	Adults and children	27/36 (75)	
Ceftriaxone, IM[30]	A	Adults and children	39/41 (95)	
Ciprofloxacin, oral[30]	A	Adults and children	70/79 (89)	
Rifampin, oral[30]	A	Adults and children	85/88 (97)	
Azithromycin, oral[31]	B (63%), A (37%)	Adults	56/60 (93)	
Rifampin, oral[31]	B (63%), A (37%)	Adults	56/59 (95)	

RR = relative risk; CI = confidence interval; IM = intramuscular; NG = nongroupable.
*RR is calculated only for the 2 placebo-controlled trials. The rest are comparative trials between ≥2 regimens.
†An analogue of sulfadiazone.

one.[27,30] In a third trial, households were randomized to different treatments, and intramuscular ceftriaxone achieved higher eradication rates than rifampin.[29] Confidence in this result, however, is reduced by its weaker, cluster randomization design. In another trial, oral azithromycin proved as effective as rifampin in eradicating meningococcal throat carriage.[31]

Harms

Minocycline: In 1 RCT, adverse effects (≥1 of nausea, anorexia, dizziness, and abdominal cramps) were reported in 36% of participants.[23] **Rifampin:** See previous "Harms" section. **Ciprofloxacin:** In trials of single-dose prophylactic regimens, no more adverse effects were reported than occurred with comparison regimens or placebo.[24,25,30] Ciprofloxacin is contraindicated in pregnancy and in children because animal studies have indicated possible articular cartilage damage in developing joints.[32] **Ceftriaxone:** No significant adverse effects were encountered in the 2 trials of ceftriaxone.[29,30] In 1 trial, 12% of participants had headache.[28] Ceftriaxone is given as a single intramuscular injection. **Azithromycin:** No serious or moderate adverse effects were reported, but nausea, abdominal pain, and headache of short duration were reported equally in the azithromycin- and rifampin-treated groups.[29]

Comment

Eradication of meningococcal throat carriage is a well-accepted surrogate for preventing meningococcal disease. It is unlikely that any RCT will be conducted on the efficacy of prophylactic antibiotics in preventing secondary community-acquired meningococcal disease in household contacts because the number of participants required would be large.

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